Exhibit B

Statement of Marvin C. Meyer, Ph.D.

To: Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane, Room 1061, Rockville, MD 20852

From: Marvin C. Meyer, Ph.D.
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College of Pharmacy, University of Tennessee Health Science Center

Re: Statement of Expert Opinion in Opposition To Shire Pharmaceuticals Group plc's 10/12/05 Citizen Petition Regarding Generic Adderall XR® (Docket No. 2005P-0420)

I hereby submit this opinion in response to Shire Pharmaceuticals Group plc's Citizen Petition dated October 12, 2005, in which Shire requests that FDA impose additional bioequivalence requirements on ANDA applicants seeking approval for generic formulations of extended-release mixed amphetamine salts products ("MASP").

Background

I am Emeritus Professor and former Chairman of the Department of Pharmaceutical Sciences and Associate Dean for Research and Graduate Programs at the College of Pharmacy at the University of Tennessee Health Science Center in Memphis, Tennessee. I received B.S. and M.S. degrees in pharmacy from Wayne State University, in 1963 and 1965, respectively. I received a Ph.D. in Pharmaceutics from the State University of New York at Buffalo in 1969. I am a registered pharmacist in Michigan and Tennessee.

Until my retirement in June 2001, I was a faculty member at the University of Tennessee for 32 years. I served as Assistant, then Associate Professor of Medicinal Chemistry and Pharmaceutics until 1976, when I became a full Professor. I became the Director of the Division of Drug Metabolism and Biopharmaceutics in 1972, then Vice Chairman and Director of the Division of Biopharmaceutics and Pharmacokinetics in 1978. I was appointed Director of Graduate and Research Programs in 1980, Assistant Dean in 1981 and Associate Dean in 1984. I became Chairman of the Department of Pharmaceutical Sciences in 1991 and held that position until I retired in 2001.

I have conducted research in the areas of bioavailability, pharmacokinetics and assay methodology, which is reflected in over 110 publications in those areas. I recently completed a three-year term as a member of the FDA's Pharmaceutical Sciences Advisory Committee and provide consulting services for a number of pharmaceutical companies.

Comments

I thoroughly reviewed Shire's Citizen Petition, including the attached exhibits. I also reviewed portions of the Adderall XR NDA and the FDA approval package for Adderall XR.

Based upon my extensive knowledge and experience in the areas of pharmacokinetics, bioequivalence, and bioavailability, I conclude that Shire's Citizen Petition has no merit. I believe that Shire does not raise any significant issue concerning extended-release MASP that would suggest that FDA should require additional studies beyond the pharmacokinetic (PK) studies ordinarily sufficient to establish bioequivalence. There is no reason to expect that a bioequivalence study conducted using a properly validated analytical method will not provide acceptable evidence of the bioequivalence of a generic and innovator dosage form of extended-release MASP.

I address, and rebut, each of Shire's arguments in favor of additional testing as follows:

A. Shire's Alleged Concerns That Adderall XR's Properties Counsel In Favor Of Additional Criteria To Establish Bioequivalence Are Misguided.

Shire cites a number of purported concerns about Adderall XR properties that, according to Shire, recommend that FDA require studies beyond traditional PK studies to establish bioequivalence. I disagree with Shire that any of these purported concerns render a PK study inadequate in the case of Adderall XR to establish bioequivalence.

1. "Superimposability": Shire argues that every ANDA applicant for a generic version of Adderall XR must show that the plasma profile concentrations are superimposable upon the plasma concentration profile described in the package insert for Adderall XR. (Shire Petition at 2-4). I disagree with Shire's contention that superimposability is required for ANDA applicants to demonstrate bioequivalence for this product.

First, Shire has shown Adderall XR to be safe and effective through the use of clinical studies. Any generic product that meets FDA's bioequivalence criteria for Cmax and AUC parameters, should also provide acceptable safety and efficacy. This is, in fact, the function of, and the foundation for, the ANDA approval process. Thus, it is not necessary for an ANDA applicant to demonstrate that the plasma profile concentrations of its generic formulation are superimposable upon the plasma profile concentrations of Adderall XR, or to conduct its own clinical trials.

Second, the fact that FDA offered to let Shire prove safety and effectiveness by showing an identical plasma concentration profile (rather than clinical studies), does not mean that a superimposability requirement should be imposed on ANDA applicants. FDA required Shire to show that the plasma concentration profile of immediate-release Adderall is identical to Adderall XR because there was no clinical evidence at the time to establish that the extended-release formulation would be safe and effective. At the time Shire sought approval for its extended-release product, only the immediate-release formulation had been tested clinically. Thus, information was not available to relate plasma concentrations to safety and efficacy. In the absence of such a reference formulation, it could not be predicted how any significant deviation from the plasma concentration-time profile for the immediate-release formulation might affect safety or efficacy. As such, FDA was concerned that there was a

"slightly different kinetic pattern between the IR and ER Adderall® formulations." (Shire Petition, Exhibit C). FDA's concern was based on the possibility that "the rate of input may be related to clinical efficacy." (*Id.*) (emphasis added).

In order to address FDA's concerns, Shire could either show superimposability or conduct clinical trials. Shire could not show superimposability and went on to conduct clinical trials, which were able to prove that the extended-release formulation was safe and efficacious. Shire's Petition, therefore, misrepresents FDA's statements and inappropriately applies FDA's concerns regarding an extended release dosage form, which had never been studied in a clinical trial, to a bioequivalence study conducted for an ANDA that references an extended-release dosage form that has been studied clinically and approved as safe and efficacious.

Third, Shire's statement that "clinical effectiveness at particular time periods is clinically important" because symptoms of ADHD occur over the course of a day is vague. Indeed, many health conditions that require drug treatment have symptoms that occur over the course of the day. Shire presents no scientific evidence to support a superimposability requirement simply because symptoms of ADHD purportedly occur throughout the day.

Fourth, Shire's statement that rate of input impacts clinical efficacy also is unsubstantiated by scientific evidence. In support of this argument, Shire relies on a study entitled "A Randomized Double-Blind, Placebo- and Active-Controlled, Crossover Study of SLI 381 in Children with Attention Deficit Hyperactivity Disorder," (Shire Petition, Exhibit D). However, this study does not actually address the need for a particular input rate. Rather, the study concludes that input must be sufficiently rapid to result in a therapeutic concentration, and this input must be continued for enough time to provide for an appropriate duration of activity. This conclusion is unremarkable and could be applied to a great number of drugs. Further, the study "observed a moderate relationship between plasma drug levels and pharmacodynamic measures for amphetamine." (Shire Petition, Exhibit D at 68) (emphasis added). This observation does not represent strong statistically significant evidence for the importance of input rate. Indeed, after reviewing Shire's NDA, FDA concluded that "[p]lasma concentrations of amphetamine are neither highly nor directly correlated with pharmacodynamic measures." (10/3/00, 5/17/01 Document from Office of Clinical Pharmacology and Biopharmaceutics Review regarding Shire NDA No. 21-303 at 1).

Finally, Shire also argues that differences in generic formulations of Adderall XR may result in formulations that are not therapeutically interchangeable. (Shire Petition at 4). This statement does nothing more than point out the importance of ensuring that generic formulations are evaluated for bioequivalence before they are deemed to be therapeutically equivalent to the reference listed product. It does not require or even suggest that FDA should impose a superimposability requirement on Adderall XR ANDA applicants.

2. Additional Partial AUC measurements: Shire's Petition suggests that ANDA applicants should conduct partial AUC measurements. In support of this proposed requirement, Shire relies on section III(A)(8)(a) of FDA's Guidance for Industry, *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations* (Mar. 2003). However, the cited discussion only relates to orally administered immediate-release, not controlled-release drug products such as Adderall XR.

Further, FDA's Guidance merely states that an early exposure measure "may be informative on the basis of appropriate clinical efficacy/safety trials and/or pharmacokinetic/pharmacodynamic studies that call for better control of drug absorption . . . ." (FDA Guidance at 8 (emphasis added)). Thus, Shire's Petition does not present any scientific evidence that partial AUC measurements are needed for a bioequivalence study using Adderall XR as a reference. Moreover, Shire's Petition presents no evidence that the traditional AUC and Cmax parameters will fail to detect a therapeutically inequivalent formulation.

Finally, Shire's clinical studies have determined that Shire's extended-release formulation is indeed safe and effective. Having established this point, Shire used conventional bioequivalence measures (Cmax and AUC) to demonstrate that its proposed extended-release formulation also was safe and effective if the capsules were opened and the contents sprinkled on applesauce before consumption. (Shire Petition, Exhibit G). Based on the documents accompanying its Petition, Shire concluded bioequivalence based on the conventional Cmax and AUC parameters only, without calculating the additional early AUC parameters or requiring that such early AUC parameters meet the stringent bioequivalence criteria demanded in the current Petition. (Shire Petition, Exhibit G). Shire reached this conclusion even though its documents demonstrate that the blood concentration profile curves of the extended-release product under fasting conditions and those after consuming the product with applesauce did not meet the superimposability test for which Shire is now asking. (Shire Petition, Exhibit G).

B. The Additional Studies That Shire Requests Should Not Be Required.

Shire requests that FDA require a number of studies to establish bioequivalence in addition to PK studies, including clinical trials in children in fed and fasted conditions. In my opinion, none of these additional studies are necessary.

1. Clinical Studies: The Petition states that clinical trials will be necessary if ANDA applicants' bioequivalence studies fail to show "identical plasma concentration-time profiles." (Shire Petition at 8). The fallacy in requiring "identical" profiles for a generic product has been discussed earlier.

Further, a clinical trial is a less precise means of assessing bioequivalence, as FDA's own regulations acknowledge. Shire does not offer any evidence or data showing that clinical endpoint studies are or would be superior to PK studies for establishing bioequivalence of a generic Adderall XR product. (Shire Pet. at 2-3, 8). Thus, Shire offers no reason for FDA to

deviate from its long-standing policies and practices, under which FDA has concluded that clinical endpoint studies should only be used when no other testing options are available. (Guidance for Industry, *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations*, at 9-10 (Mar. 2003)). As I discussed above, a PK study would be sufficient to establish bioequivalence and thus clinical studies should not be used.

2. Studies on Children: Shire suggests that ANDA applicants must conduct clinical studies on children because the pharmacokinetics of children differ from that of adults. (Shire Pet. at 8). I do not believe that the differences that Shire cites between adults and children precludes the use of adults as subjects in bioequivalence testing.

It is well known that the pharmacokinetics of a drug can differ in adults and children. A number of drugs are indicated for use in children, but FDA does not require bioequivalence studies on those drugs to be conducted in children despite the differences in metabolism and PK. This does not mean that the bioequivalence of all drugs that are useful in children must be studied in children and adults. In fact, it is unlikely that two products that are bioequivalent in adults will not be bioequivalent in children.

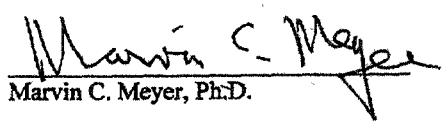
Further, Shire has relied on studies conducted using healthy adult subjects to establish bioequivalence and bioavailability. FDA concluded that those studies were "acceptable" to establish the RLD's bioavailability. For example, the study conducted by Shire to determine the effect of food only utilized adults aged 18-55 years old, yet Shire's package insert does not distinguish between adults and children with regard to the effect of food. (*See* Shire Petition at Exhibits A and G). Shire offers no data that would demonstrate that testing on children is necessary, and has, itself, used adults to establish bioequivalence and bioavailability for the RLD. The fact that the pharmacokinetics of Adderall XR differs in children and adults would not be relevant to a bioequivalence study with a crossover design.

Finally, although FDA recommends conducting PK studies in children in order to determine the appropriate dose level to use in clinical safety and efficacy studies (*see* Draft Guidance, *General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products*, at 4 (Nov. 1998)), nothing would warrant subjecting young children (some as young as six years old) to the discomfort of extensive blood sampling as part of an additional and unnecessary PK study.

Conclusion

For the reasons discussed above, I do not believe that FDA should credit any of Shire's arguments.

Respectfully submitted,



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